REMARKS

I. Status of the Claims

Claims 18-22, 28, 29, 31, 32 and 34-67 are pending in the application. The claims stand rejected under 35 U.S.C. §112, 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants note that in their response to restriction requirement, a request for interview was made. However, the examiner did not call the undersigned upon receipt of applicants' previous response. Applicants respectfully request, again, that upon consideration of this response, the examiner contact the undersigned to discuss any remaining issues.

II. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 18-22, 28, 29, 31, 32 and 34-67 stand rejected under the second paragraph of §112 as indefinite. The specific rejections are traversed generally, but are addressed as follows:

- Claim 18 – "essentially unprimed"; the word essentially has been dropped
- Claim 28 – "functionally rearranged"; the language has been dropped
- Claims 34 and 36 – "at least one CDR"; the language has been dropped
- Claim 66 – "derived"; the language has been dropped
- Claims 22 and 32 – "correspond" and "comprises", respectively; the objected terms have been replaced by "encoded by"

In light of the preceding, applicants respectfully request reconsideration and withdrawal of the rejection.

III. Rejections Under 35 U.S.C. §112, First Paragraph

A. Enablement

Claims 18-22, 28, 29, 31, 32 and 34-67 stand rejected under the first paragraph of §112 as lacking an enabling disclosure. The examiners' concerns can be place into three categories: (a) that the claims encompass non-functional antibody fragments; (b) that the claims read on *in vivo* embodiments since "pharmaceutical compositions" are claimed; and (c) that the claims do not specifiy the antigen to which it binds. With respect to (c), applicants have amended claim 18, the only claim lacking a specific target recitation, to recite binding of the receptor to native human 17-1A antigen. With regard to (a) and (b), applicants provide the following.

The examiner is quite correct in arguing that changes in receptor structure can drastically alter receptor function, and that short pieces of an antibody containing less than six CDR's might well not work as intended. However, it is an improper interpretation of the claims to find that they read on such non-functional fragments. First, claim 18 states that the receptor (now antibody) comprises both VH and VL chains. ***By definition***, these molecules ***must*** contain a total of six CDR's. The fact that dependent claims might speak to fragments cannot change the fact that dependent claims only ***further limit*** the subject matter of the independent claims, so any fragments would ***also*** containing, by defintion, six CDR's.

Turning to the remaining issue, set forth in (b) above, applicants traverse. The examiner has argued that the inclusion of the term "pharmaceutical composition" in claims 38, 39, 42, and 53-56 renders these claims non-enabled as they "read on *in vivo* treatment of cancer." No legal authority is cited for this position, nor could there be based upon a proper application of the controlling law. In the absence of a relevant case law citation, applicants provide the following.

The examiner has acknowledged that certain aspects of the present invention are enabled for *in vitro* uses – hence, claim 18 and other antigen receptor claims are not rejected. However, the inclusion of this antibody in a pharmaceutical composition does not mean that this antibody ***must*** be used *in vivo*, as argued by the examiner in rejecting the pharmaceutical composition claims. Rather, the examiner is reading an intended use into these claims – something the PTO clearly views as improper.[1] So, instead of implying methodologic limitations into composition claims, the examiner should simply apply a proper enablement analysis.

The appropriate questions in determining whether a pharmaceutical composition claim is enabled are (a) "Can one make the pharmaceutical composition?"; and (b) "Can one use the pharmaceutical composition?" Certainly, one cannot argue that combining the antibody of claim 18 with a pharmaceutically acceptable carrier is not enabled. As far as use, it is not required that each and every possible use be enabled, only that a single use be enabled. Thus, because the pharmaceutical compositions ***can*** be used *in vitro* in just the same way as the antibody of claim 18, their use also is enabled. Further, there is no reasoning provided as to why formulation of the pharmaceutical compositions would rob them of their *in vitro* use. Thus, on the record, the rejection clearly is improper.

However, in order to make the record complete, applicant is submitting a copy of Naundorf *et al.* (2002) (attached), which describes the *in vivo* activity of an anti-17-1A antibody.[2] As discussed in the abstract, "[i]n a nude mouse xenograft model, growth of tumors derived from the human colon carcinoma line HT-29 was significantly and comparably

[1] See Office Action at page 13, lines 3-4: "The intended use as a pharmaceutical composition is given no patentable weight ...." The PTO cannot have it both ways.

[2] The equivalence of the Naundorf *et al.* antibody, MT201, also designated HD69 therein, to the antibodies of the claimed invention, may be ascertained by reference to Raum *et al.* (2001) (attached), which discusses that HD69 was made by precisely the same steps as the antibodies of the present invention.

suppressed by MT201 and edrecolomab [Panorex®]." Further support for the *in vivo* use of the claimed invention derives from Xiang *et al.* 2003) (attached), which shows that MT201 is cytotoxically active in an *ex vivo* lysis assay using primary ovarian tumor cells. Together, these data provide *prima facie* evidence that the antibodies of the present invention have use in *in vivo* settings. Thus, even if one were to examine the present claims under an enablement standard similar to that of a therapeutic method, the claims would still satisfy §112, first paragraph.

In light of the foregoing, applicants respectfully request reconsideration and withdrawal of the rejection.

B. Written Description

Claims 18-22, 28, 29, 31, 32 and 34-67 stand rejected under the first paragraph of §112 as lacking a sufficient written description. The examiner states that the specification only discloses antibodies, not "antigen receptors" as broadly claimed, does not disclose receptors to "a multitude of antigens," and does not describe "functionally rearranged VH or VL." First, though not necessary, applicants have amended the claims to recite antibodies rather than antigen receptors. Second, the claims now all recite that the target for the claimed antibodies is native human 17-1A antigen. And third, the claims have been amended and no longer recite "functionally rearranged." In light of these amendments, reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. §102

A. U.S. Patent 5,885,793

Claims 18-20, 28, 29, 34-40, 43-45, 48-50, 53, 54, 65 and 67 are rejected as anticipated by the '793 patent. Applicants traverse. Each claim now recites that the claimed antigen

receptor recognizes native human 17-1A antigen. The '793 patent only describes antibodies to CEA, and does not mention human 17-1A. Therefore, the rejection is improper and should be withdrawn.

B. U.S. Patent 6,150,584

Claims 18-20, 34-40, 43-45, 48-50, 65 and 67 are rejected as anticipated by the '584 patent. Applicants traverse. Each claim now recites that the claimed antigen receptor recognizes native human 17-1A antigen. The '854 patent does not even mention human 17-1A, and thus cannot possibly anticipate these claims. Therefore, the rejection is improper and should be withdrawn.

C. Hoess et al.

Claims 18-21 and 34-37 stand rejected over Hoess *et al.* ("Hoess"). As discussed by the examiner, Hoess indeed teaches antibodies which bind human 17-1A antigen. However, the examiner is wrong in stating that Hoess describes antibodies that bind to ***native*** human 17-1A, and on this basis, applicant traverses.

A careful review of the reference will reveal that Hoess tests antibodies produced from a combinatorial library, having two different specificities – for 17-1A and LeY. Although antibodies that bound 17-1A were identified, these antibodies bound only to ***immobilized antigen*** and did not recognize cancer cells. To the contrary, the anti-LeY antibodies ***did*** reocognize cancer cells. This distinction indicates that the antibodies to 17-1A did ***not*** recognize native antigen, and thus, could not anticipate the presently claimed invention. In further support of this position, applicant points to De Kruif *et al.* (1995) (attached), at page 101, which states "None of the MoPhabs against ICAM-1 or δEGP-2 displayed binding to cells expressing these

molecules ...." Thus, this reference teaches that these researchers failed to generate and isolate an anti-17-1A (there called EGP-2) antibody that recognized the native antigen.

Thus, based on the evidence of record, applicant submits that Hoess does not anticipate the invention as now claimed. Reconsideration and withdrawal of the rejection is therefore requested.

V. Rejections Under 35 U.S.C. §103

A. The '793 Patent in view of Gottlinger et al.

Claims 18-21, 28-31, 34-41, 43-46, 48-51, 53-55, 57-59, 61-63, 65 and 67 are rejected as obvious over the '793 patent in view of Gottlinger *et al.* ("Gottlinger"). Applicants traverse.

The '793 patent, as discussed above, does not disclose anything regarding the 17-1A antigen. Rather, it describes a method for the production of anti-self antibodies against self-antigens such as MUC1, carcinoembryonic antigen (CEA), recombinant soluble CD4, human thyroglobulin and TNFα. The expression of all those self-antigens in normal tissue is somewhat restricted, however, as evidenced for CEA. "CEA was not ubiquitously expressed (Fig. 2)" (Eades-Perner *et al.*, 1994, *Cancer Res* 54(15), at page 4171, first few lines of first full para.) (attached). Further, normal (non-cancerous) tissue of the pancreas tested negatively for CEA (see Allum *et al.*, 1986, , *J. Clin. Pathol.* 39, at page 612, Table 2, and page 612, left column, last para.) (attached).

In contrast thereto, the ubiquity of 17-1A antigen expression has been discussed in the instant patent application (see passage extending from page 14, last para., line 3 from bottom, to page 15, 1st para., line 5) where it had been stated:

> Among the known tumor associated antigens 17-1A is by far more ubiquitously expressed on a broad range of normal epithelial tissues than other tumor antigens, in addition to its expression on epithelial tumors. Therefore, the 17-1A-antigen is currently regarded to represent a pan-epithelial antigen rather than a tumor antigen... In comparison, other so called tumor antigens found on epithelial tumors, like erb-B2 (Her/neu), Muc1 (PEM) or the Thompson-Friedenreich-antigen usually show a much more restricted expression pattern on normal epithelial tissues.

Due to the ubiquity of 17-1A antigen and the selective force of self tolerance, which controls the formation of such self-reactive antibodies within the human body, it is extremely difficult to generate human antibodies against the native 17-1A antigen. As described at page 15, lines 5-12, of the corresponding WO publication:

> Thus the selective force of self tolerance against B-lymphocytes expressing 17-1A reactive antibodies even with low affinity is expected to be exceptionally high, since it appears nearly impossible for such B-cells to avoid encounters with the 17-1A antigen for longer periods of time, due to the ubiquity of this antigen. Therefore, it was surprisingly found in accordance with the present invention, that 17-1A specific antibodies... can be isolated from the antibody repertoire of human B-cells....

In this context, reference is made to the argument presented above regarding Hoess *et al.* Both that publication, as well as De Kruif *et al.*, report that their human anti-17-1A antibodies only recognized immobilized recombinant antigen, and failed to recognize the native antigen on tumor cells.

Thus, these reports support the view that creating antibodies to 17-1A that are reactive with the native antigen was a very difficult and thus unpredictable endeavor. Thus, the subject matter of claims 18 and 28, as well as all claims that depend thereon, cannot possibly be considered obvious in light of the well-documented problem of obtaining human 17-1A antibodies that recognize the native antigen on tumor cells. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. The '584 Patent in view of Gottlinger et al

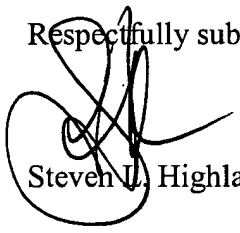
Claims 18-21, 34-41, 43-46, 48-51, 65 and 67 are rejected as obvious over the '584 patent in view of Gottlinger. Both references are cited as above. Applicants once again traverse.

This rejection effectively mirrors that advanced above in view of the '793 patent and Gottlinger. And thus, for the same reasons given above, the rejection fails due to the difficulty, and hence lack of predictability, of creating human anti-17-1A antibodies. Reconsideration and withdrawal of this rejection is requested as well.

VI. Conclusion

Should Examiner Helms have any questions regarding this response, a telephone call to the undersigned is invited. Please date stamp and return the enclosed postcard as evidence of receipt.

Respectfully submitted,



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